REMARKS

Claims 75, 95, 99-101, 104-112, 121, 122, and 129-132 were pending in the instant application. By this amendment, claims 75, 97, 111, 112, 122, 129, and 132 have been amended, claims 104-110, 121, 103, and 131 have been canceled, without prejudice to applicants' right to pursue the canceled claims in other applications, and new claims 133-147 have been added to recite a method for inhibiting re-presentation of an antigenic peptide. In addition, claims 111, 112, 122, 129, and 132 have been amended to correct claim dependency, in light of the claim cancellations and amendments.

The amendments and new claims are fully supported by the specification of the application as originally filed, as follows. Support for the amendment to claim 97 can be found at: page 7, lines 19-23; page 51, lines 20-25 and 33-36; page 52, lines 1-4 and 28-35; and page 17, lines 12-13. Support for new claim 133 and 139 with respect to inhibiting re-presentation is found at page 82, lines 34-36, and page 15, line 13. Support for new claim 134 is found at page 7, lines 19-23. Support for new claims 135-137 is found at page 17, lines 8-11. Support for new claim 138 is found at page 51, lines 24-26 and page 32, lines 27-30. Support for new claim 140 is found at page 69, line 30 through page 70, line 10. Support for new claim 141 is found at page 10, line 1. Support for new claim 142 is found at page 27, line 19. Support for new claim 143 is found at page 9, lines 27 and 34. Support for new claims 144-147 is found at page 25, lines 15-20 and page 26, line 9 through page 27, line 32. As such, no new matter has been added.

Thus, claims 75, 97, 99-101, 111, 112, 122, 129, 132 and 133-147 are pending in the instant application.

1. THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR LACK OF WRITTEN DESCRIPTION SHOULD BE WITHDRAWN

Claim 121 is rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. In particular, the Examiner contends that the specification does not provide evidence of, or recite a specific utility for, any agonist that is capable of binding or modulating the interaction between α2M receptor and its ligand.

In response, claim 121 has been canceled without prejudice. In light of the cancellation of claim 121, the rejection under 35 U.S.C. § 112, first paragraph for lack of written description has been obviated and should be withdrawn.

2. THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, FOR INDEFINITENESS SHOULD BE WITHDRAWN

Claims 75, 97, 99-101, 104-112, 121-122, and 129-132 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Applicants believe these rejections are overcome and/or obviated by the foregoing amendments and remarks below.

The test of definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. *Orthokinetic Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1 U.S.P.Q.2d 1081 (C.A.F.C. 1986). Thus, according to applicable case law, the requirement of 35 U.S.C. § 112, second paragraph, means that the claims must have a clear and definite meaning when construed in the light of the complete patent document. *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 227 U.S.P.Q.

293 (C.A.F.C. 1985).

Regarding claims 75, 104-105, 107, 110, and dependent claims thereon, the Examiner contends that the terms "preventing" and "prevent" are unclear. In response, claim 75 has been amended to delete recitation of "prevent," and claims 104, 105, and 107 have been canceled. With respect to new claim 139 which recites "prevent," it is clear from the claim that prevent means inhibiting the re-presentation of antigenic peptides thereby blocking an immune response of an autoimmune disorder. Thus, the rejection for indefiniteness with respect to the term "prevent" has been obviated and/or overcome and should be withdrawn.

Regarding claims 75 and 105, and dependent claims thereon, the Examiner contends that the term "effective amount" is unclear. The Examiner contends that the metes and bounds of the claim cannot be determined because any amount can be considered effective. Applicants respectfully disagree that the term "amount effective to treat an autoimmune disorder" renders the claims indefinite.

The Examiner is directed to MPEP § 2173.05(c):

> The common phrase "an effective amount" may or may not be indefinite. The proper test is whether or not one skilled in the art could determine specific values for the amount based on the disclosure. See *In re Mattison*, 509 F.2d 563, 184 USPQ 484 (CCPA 1975). The phrase "an effective amount . . . for growth stimulation" was held to be definite where the amount was not critical and those skilled in the art would be able to determine from the written disclosure, including the examples, what an effective amount is. *In re Halleck*, 422 F.2d 911, 164 USPQ 647 (CCPA 1970). . . . The more recent cases have tended to accept a limitation such as "an effective amount" as being definite when read in light of the supporting disclosure and in the absence of any prior art which would give rise to uncertainty about the scope of the claim. In *Ex parte Skuballa*, 12 USPQ2d 1570 (Bd. Pat. App. & Inter. 1989), the Board held that a pharmaceutical composition claim which recited an "effective amount of a compound of claim 1" without stating the function to be achieved was definite, particularly when read in light of the supporting disclosure which provided guidelines as to the intended utilities and how the uses could be effected.

The legal standard of definiteness, as it applies to the term "effective amount," supports applicants' position regarding the definiteness of the term "amount effective to treat

an autoimmune disorder." In particular, Section 5.10.1 at page 72, line 11-31 of the specification discloses the efficacy of compounds used in the methods of the invention. Contrary to the Examiner's contention, it is not any amount, but rather the amount is dependent on and limited by numerous factors such as the route of administration, frequency of administration, size of subject, or lethality of the method. Methods for determining effective amounts based on animal models are also disclosed which do not require extensive experimentation. When considered in light of the specification, which provides ample guidelines as to the intended utilities of anti-CD91 antibodies and how these uses could be effected (see, for example, page 51, lines 19-31), one of skill in the art can readily determine what is an amount effective to treat an autoimmune disorder. Thus, in view of the description in the specification and applicable case law, the phrase "amount effective to treat or prevent and autoimmune disorder," has a definite meaning to the skilled artisan.

Regarding claims 97, 105, 108 and 111, and dependent claims thereon, the Examiner contends that the term "modulate" is unclear. In particular the Examiner contends it is unclear whether this term represents inhibition or enhancement of activity. In response, claims 105, 108, and 111 have been canceled, claim 97 has been amended to replace the term "modulate" with "interferes with" (page 7, lines 19-23).

Regarding claims 105, 108, and 111, and dependent claims thereon, the Examiner contends the recitation of the term "ligand" is unclear as to which ligand is being referred and thus the metes and bounds of the term allegedly cannot be determined due to the multitude of ligands that can interact with CD91. In response, claims 105 and 108 have been canceled without prejudice and claim 111 has been amended to replace "alpha (2) macroglobulin receptor ligand" with "alpha (2) macroglobulin." In view of the amendment, the rejection has been obviated with respect to the clarity of the term ligand.

Regarding claims 97, 99, 100, and 101, the Examiner contends that the term

"heat shock protein" is unclear as to what type of heat shock protein is being referred and thus the metes and bounds of the term cannot be determined because there are numerous possible HSPs. Furthermore, the Examiner contends that the terms "gp96", "Hsp70", and "Hsp90" are unclear with respect to human or bacterial origin.

Applicants respectfully disagree with the Examiner's contention. A myriad of heat shock proteins can be used in the methods of the instant invention, regardless of their origin. In particular, applicants have demonstrated the interaction of CD91 and several species of heat shock proteins, *e.g.*, gp96, hsp70, and hsp90 (see specification, Figs. 9B and C, and description thereof). Moreover, the specification provides numerous other species of heat shock proteins which can also be used with the methods of the instant invention. As disclosed in the specification, heat shock proteins are a highly conserved class of proteins, both structurally and functionally (page 1, line 34 through page 2, line 5). The instant specification defines the genus of heat shock proteins which can be used for the methods of the instant invention, both by their functional and structural characteristics (see page 1, lines 25 through page 2, line 15 of the application as filed). Thus, the term "heat shock protein," as used in the context of the claims and in light of the disclosure in the application, has a clear and definite meaning.

In view of the reasoning and examples presented above, applicants submit that the claims are not indefinite within the meaning of 35 U.S.C. § 112, second paragraph and the rejection should be withdrawn, and request withdrawal of the rejection for indefiniteness.

3. THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR ENABLEMENT SHOULD BE WITHDRAWN

Claims 75, 97, 99-101, 104-112, 121-122, and 129-132 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it

pertains, or with which it is most nearly.connected, to make and/or use the invention. In particular, the Examiner contends that the claimed methods of treatment and prevention are not enabled because one skilled in the art would have to engage in undue experimentation as the specification has not taught how to accomplish treatment or prevention of proliferative disorders, infectious diseases, or autoimmune diseases, or how to use an enhancing antibody. Applicants respectfully submit that the claims, as amended, are fully supported and enabled by the specification as described in detail below.

The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *U.S. v. Telectronics Inc.*, 857 F.2d 778, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988). Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover*, 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). The factors that can be considered in determining whether an amount of experimentation is undue have been listed in *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, so long as it is merely routine. *Id.*

Working examples are not necessary to meet enablement requirements and that lack of examples should not be equated with lack of direction. "Nothing more than objective enablement is required, and therefore it is irrelevant whether the teaching is provided through broad terminology or illustrative examples." *In re Marzocchi*, 439 F 2d 220.

Finally, case law has resolved that not all embodiments of an invention need be effective. The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v E. I. Du Pont* 750 F2d. 1569.

In light of the legal standard discussed *supra*, applicants submit that the claims, as amended, are enabled by the instant specification. The instant application provides sufficient teaching to enable one of skill in the art to make and use the methods of the invention which involve administering an anti-CD91 antibody that binds alpha (2) macroglobulin receptor to treat or prevent an autoimmune disorder, without undue experimentation, as described below.

First, according to the Examiner, the specification lacks enablement of methods for treatment or prevention of infectious disease and cancer or for an enhancing antibody that is capable of acting as an agonist. In response, claim 75 has been amended to delete methods for treating and preventing infectious disease and cancer, and methods for preventing an autoimmune disorder. Thus, amended claim 75 and claims dependent thereon now encompass only treatment of an autoimmune disease.

In response to the Examiner's rejection of the use of an enhancing antibody that is capable of acting as an agonist, the rejection is no longer applicable to claims 97 and 111, which have been amended to replace "modulate" with "interferes with," and thus no longer encompass enhancing antibodies. With respect to claim 75, applicants point out that sufficient numbers of antibodies to CD91 should be operative in the claimed method so as to enable the genus of recited antibodies.

Secondly, the Examiner further contends that a method for treating or

preventing an autoimmune disorder would require undue experimentation because the specification had not taught how to accomplish such a method. Applicants respectfully disagree and assert that the specification provides ample disclosure to enable one skilled in the art to treat or prevent an autoimmune disease using the claimed methods without resorting to undue experimentation.

The specification teaches that treatment of autoimmune disorders and conditions is accomplished by administration of a compound, such as an antibody, that interferes with the ligand-alpha (2) macroglobulin receptor interaction to block an immune response. This treatment, based on blocking antigen uptake and re-presentation, can be achieved in various ways, including by using antibodies specific to a ligand or the receptor that interfere with binding of the ligand to the receptor, or antibodies that competitively inhibit binding of the ligand and receptor (see page 51, lines 22-26; and page 51, line 33 through page 52, line 4). Methods for formulations and determining effective dosages of such therapeutics are also disclosed in the instant specification (see page 72, line 3, to page 74, line 18).

Furthermore, the specification teaches how to accomplish treatment of autoimmune disorders in the context of treatment in general, at page 51, lines 10-16:

> In particular, as described in detail hereinbelow, recombinant cells comprising α2M receptor complexes, such as HSP-antigenic peptide complexes, *antibodies* and other compounds that interact with the α2M receptor, or modulate the interaction between the α2M receptor and its ligands, *e.g.*, HSP, as well as other compounds that modulate HSP-α2M receptor-mediated processes may be used to elicit, or block, an immune response to treat such HSP- α2M receptor-related disorders and conditions. [*Emphasis added.*]

"HSP-α2M receptor-mediated processes" as described in the specification include antigen presentation (see page 13, line 3) and "HSP-α2M receptor-related disorders" as described in the specification include autoimmune disorders, see page 7, lines 11 and 12.

Thus, the specification clearly teaches how to accomplish treatment of an autoimmune disease by administering an antibody that blocks re-presentation of antigenic peptides and blocks an immune response, thereby treating an autoimmune disorder.

Since one skilled in the art would understand that an autoimmune disease is characterized by an immune response, blocking such responses, as taught in the specification, would be recognized by the skilled artisan as means of treatment or prevention. Treatment and prevention of disorders is taught at page 11, lines 23-25, and disorders are described as including autoimmune disorders in the context of the invention, see page 7, lines 11 and 12. Interfering with the ligand-alpha (2) macroglobulin receptor interaction would be predicted to block broadly the immune responses that result from receptor interactions. Thus, it would not be necessary to identify antibodies that act specifically on a particular immune response, and such undue experimentation would not be needed. Following the teachings of the specification, one skilled in the art should be able, without undue experimentation, to make anti-CD91 antibodies and administer them to block an immune response, thereby treating or preventing an autoimmune disease.

Thirdly, the Examiner contends the specification has not taught how to utilize, treat, or prevent disease through manipulation of the CD91/alpha (2) macroglobulin receptor-HSP interaction. In particular, the Examiner contends that the specification only provides an *in vitro* experiment teaching the ability of a peptide to be blocked or presented by an MHC class I molecule. Moreover, the Examiner further contends that undue experimentation would be required to prevent autoimmune disorders because the patient population to be treated or vaccinated is unknown. Applicants respectfully disagree, and submit that the *in vitro* data present in the specification (see Examples in Section 6, pages 74-87 and Figures 4, and 9B and 9C) reasonably correlates with the asserted utility and thus meets the utility standard under 35 U.S.C. § 112, first paragraph.

Finally, with respect to the Examiner's contention that one skilled in the art would not be able to identify the patient population for prevention of autoimmune disease, applicants assert that one skilled in the art would be able readily to identify mammals at risk for development of autoimmune disease. Applicants submit herewith references to illustrate the availability of such information to the skilled artisan (Tait, 1990, J. Autoimmunity 1:3-11, submitted herewith as Information Disclosure Statement (IDS) reference #EU, hereinafter referred to as "Tait"); Wong *et al.,* 1991, Clinical Experimental Immunology 83:69-73 (submitted herewith as IDS #EV), hereinafter "Wong"; Sotgiu *et al.*, 1998, Acta Neurologia Scandinavica 98:314-317 (submitted herewith as IDS #ET), hereinafter "Sotgiu"; Epplen *et al.*, 1997, Annals of Neurology 41:341-352 (submitted herewith as IDS #ES), hereinafter "Epplen". Tait discloses that the underlying cause of type I diabetes is an autoimmune response precipitated by both environmental and genetic factors. Tait also discloses that HLA genes are involved in susceptibility to type I diabetes and that there is a correlation to susceptibility and an individuals sequence of HLA genes and that such sequences can be used as markers of susceptibility and to determine risk, see page 8, seventh paragraph. Wong demonstrated that the CD3 epsilon locus is associated with type I diabetes in women, see page 71, first paragraph of discussion. Sotgiu disclose that an individuals susceptibility to multiple sclerosis correlates to inherited alleles of HLA-genes, see page 316, last paragraph. Epplen disclose that HLA-DRB1 and TCR genes correlate to multiple sclerosis susceptibility and that immunization schemes may be designed based on the findings, see page 351, first paragraph. Thus, one skilled in the art would clearly have been able to identify individuals with susceptibility to various autoimmune disorders and administer the methods of the invention to prevent such disorders, given the susceptibility markers readily available in the art.

In view of the forgoing arguments and amendments, one skilled in the art

would be able to use the claimed methods to treat or prevent an autoimmune disease in a mammal, given the teachings of the specification, without needing to resort to undue experimentation. As such, applicants respectfully request the Examiner's withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

CONCLUSION

Applicants respectfully request that the present remarks and amendments be entered and made of record in the instant application. It is submitted that all the outstanding rejections should be withdrawn. An allowance of the application is earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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